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THE DISTRIBUTION AND BEHAVIOUR OF CUTANEOUS NERVES IN NORMAL AND ABNORMAL SKIN.

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ALTHOUGH the anatomical distribution of nerves to most areas of the body has been generally understood for many years, the behaviour of the nerve supply, including sensory and autonomic fibres, to the skin has not been finally determined. The form of sensory terminations originally described by Von Frey, and thought by implication to refer to the entire skin, has recently been seriously questioned by several investigators. The functional behaviour of the cutaneous nerves poses an even greater problem in the physiological field of dermatological research.

One of the focal problems is the question of impulse transmission between receptor (or effector) organ and the nerve. As long ago as 1879, Hermann proposed a theory of electrical transmission along the nerve fibre by means of a current flow. Elliott, in 1904, conceived the idea of a chemical transmitter, subsequently identified as acetylcholine by Dale *et al.* Through their work on the chemicals released at nerve endings, this latter group, and also Cannon and his associates, did much to strengthen the concept of chemical transmission by means of acetylcholine and epinephrin (or *nor*-epinephrin). After the discovery that acetylcholine was released at the nerve ending of the neuromuscular synapse, these workers detected the release of the same substance or of epinephrin at the terminations of other motor nerves ; Dale (1934) then proposed a classification of motor nerve fibres, including autonomic ones, into cholinergic

and adrenergic types, depending upon which of these two chemicals was released from their environs. It was believed that the nerves supplying the sweat glands were cholinergic, while those to the cutaneous blood vessels were adrenergic in type. This working hypothesis was not seriously questioned until Lewis (1927) suggested the existence of cutaneous vasodilator nerves. The triple response in skin, which was the subject of his study, manifested itself by a vasodilatation about the area of stimulation ; such an effect required the presence of nerves capable of causing vasodilatation. Since this function could not be ascribed to those sympathetic adrenergic fibres known to exist, Lewis had to introduce the theory that the vasodilatation occurred by means of sensory nerves, carrying antidromic impulses, or by autonomic vasodilator fibres following the same pathways as sensory nerves. Since the clinical form which is assumed by the triple response contributes to the diagnostic armamentarium of the physician, the physiological explanation of such a mechanism is important.

Besides the chemical release at nerve terminations, it has been proposed by recent investigators, especially Nachmansohn (1946), that the actual transmission of the nerve impulse through the substance of the fibre, either sensory or motor, is effected by the alternate release and breakdown of acetylcholine by its specific enzyme acetylcholinesterase, and its reconstruction by choline acetylase. Both these enzymes have been identified in nerve fibres, and it is generally thought that their presence in the membrane of the nerve fibre is concerned to a great extent with transmission, although impulse propagation may not depend directly on their chemical alteration.

The recently introduced method of *in vivo* staining of nerve fibres by means of hyaluronidase and methylene blue has proved a dependable means of identifying cutaneous nerves, and Koelle's histochemical staining technique has permitted the visualization of deposits of acetylcholinesterase (the specific enzyme) and non-specific cholinesterase. Thus, in recent years, we have had at our disposal two methods by which it might be possible to investigate the questions discussed above.

Our present research attempted to study the problem of cutaneous innervation under the following headings :

(i) An anatomical description of the nerve supply to the skin ; in particular the form of sensory terminations, the innervation of the skin appendages, and the supply to the small arterioles.

(ii) The involvement of the acetylcholine-acetylcholinesterase system in the function of these nerves in the normal skin.

(iii) The role of this chemical system in some skin responses.

(iv) Variations in the anatomical and physiological behaviour of nerve fibres in several dermatoses—psoriasis, eczema, urticaria, and atopic dermatitis—including their responses to test situations.

Material and Methods.

Patients who volunteered for these investigation included :

(*a*) Thirty-one with normal skin.

(*b*) Ten of the above group, in whom an additional small area of skin was exposed to an erythema-producing physical agent, e.g. ultra-violet, thorium-X, or Grenz irradiation.

(*c*) Ten normal patients in whom small areas of skin were exposed for a 2-minute period to cold or heat.

(*d*) A group of patients with various dermatoses, including 10 with psoriasis, 53 with eczema, 31 with atopic dermatitis, and 14 with urticaria—8 of these presented the clinical criteria ordinarily accepted for the diagnosis of cholinogenic urticaria (Grant *et al.*, 1936).

Sites tested included the back, arms and legs, but not the face, palms or soles.

Morphology.—The methylene blue-hyaluronidase nerve stain, as introduced by Weddell (1950), was used to trace the microscopic anatomy of the cutaneous nerves. Briefly, this consisted of the introduction of a local anaesthetic, followed in 5 minutes by the intradermal injection of 0·1 ml. of a solution of 0·5% methylene blue and 150 units of hyaluronidase in normal saline. Biopsy was done 20 minutes later, and the tissue transferred directly to an aqueous solution of ammonium molybdate (8%) for 8 hours. Frozen sections were then cut for examination.

Histochemistry.—A portion of the excised tissue was stained using Gomori's modification of Koelle's stain for cholinesterases (Koelle and Friedenwald, 1949 ; Koelle, 1950). No prior fixation was used for most of the specimens, but in a few cases 4% formalin in M/15 phosphate buffer was used during transport of the material. Intervals of up to 1 hour in such a solution did not alter results, but longer periods appeared to destroy the enzyme.

In this method two substrates were used for each specimen examined ; these were acetylthiocholine, which may serve as a substrate for both acetylcholinesterase and non-specific cholinesterase, and butyrylthiocholine, which acts as a substrate for the latter enzyme only. In each case, the action of the enzyme on its respective substrate produces a deposit of copper thiocholine at the site of the enzyme activity, and this substance is in turn converted to copper sulphide, which is visualized as a black aggregate. A third consecutive section was pretreated with eserine (an anti-cholinesterase), and a fourth was incubated in the stock solution alone. The two latter sections served as controls.

Twenty mg. of the substrate was dissolved in a drop of distilled water, and 10 ml. of stock solution* was then added. Sections were incubated in the resultant solution for periods up to 4 hours, washed in distilled water, dried, and immersed in dilute ammonium sulphide. Sections were counterstained with eosin 0·5%, dehydrated, and mounted.

Intradermal tests were carried out in a number of these subjects, including 30 normal controls, 10 normal patients previously treated with an erythema-producing agent (e.g., ultra-violet irradiation), 30 eczematous patients, 30 with atopic dermatitis,

* Formula of stock solution :

Hydrous copper sulphate	0·3 G.
Glycine	0·375 G.
Magnesium chloride ($MgCl_2.6H_2O$)	1·0 G.
Maleic acid	1·75 G.
Hot saturated solution of sodium sulphate	170·0 ml.
1 N sodium hydroxide	30·0 ml.

The pH of this solution was 6·0. In the later work acetate buffer was used to give a pH of 4·2. At this level, there was no change in the enzyme staining, but the background stain was minimal.

and 14 with urticaria. The test substances included acetylcholine (1/10,000 in saline), histamine (1/100,000), atropine (1/1000), nicotine (1/10,000), prostigmine (1/10,000), and Trafuril Cream (Thurfyl nicotinate) (5%). The first five materials were administered by injection in 0·1 ml. doses ; Trafuril was used as a local application. Biopsies were performed at the sites of the cutaneous responses to these agents, and treated as outlined above.

Results.

The Microscopic Anatomy of Cutaneous Nerves.

Normal skin.—No specialized form of nerve ending was observed in any of the sections studied ; all the cutaneous nerves appeared to terminate simply as free fibrils, in one of five sites :

(i) Larger fibres, traced from the deeper into the more superficial layers of the dermis, ended here after division of their finer branches.

Fig. 1.—Arborizing nerve fibres about an eccrine sweat gland. A number of separate branches contribute to the supply. Methylene blue. × 200.

(ii) In the superficial dermis, branches from the above nerves sent prolongations into the epidermis between the basal cells to terminate in the stratum germinativum or stratum granulosum.

(iii) Certain of the terminating dermal fibres were traced to positions immediately contiguous to the small arterioles ; none were directly observed to enter the vessel walls.

(iv) Arborizing fibres surrounded the bases of hair follicles.

(v) Fine ramifications of nerves occurred about the sweat glands, and prolongations of these branches could be traced along the coiled ducts of the glands for a short distance (Fig. 1).

Except for the absence of the nerve supply to the sweat glands, there was no alteration from this form of neural distribution in the skin of four patients who had been, for various reasons, subjected to sympathetic denervation of the areas tested.

Abnormal skin.—No variation was observed from the preceding description in sections examined from patients suffering from psoriasis, eczema, urticaria, or atopic dermatitis, or in those whose skin had been pretreated in any of the ways outlined.

Histochemical Study of Superficial Cutaneous Nerves.

Although this method of staining purports to differentiate between specific and non-specific types of cholinesterase, the present attitude amongst pharmacologists and biochemists suggests that the cholinesterases as a group are interrelated, and that no strict separation is possible. Consequently, in the following outline of our results, we have not attempted to label the identified enzyme definitely although in the discussion the probable exact nature will be suggested.

Normal skin.—By the use of Koelle's stain, correlated with the Weddell method of nerve staining, enzyme particles were observed in four sites :

(i) Linear threads of enzyme were occasionally noted along the nerve fibres in the dermis, always stopping short of the terminal points.

(ii) Aggregations of particles in and around the walls of some of the smaller arterioles.

(iii) Arborizing linear deposits about the eccrine glands, exactly corresponding to the stained nerve fibres (Fig. 2). No such staining was noted about the apocrine glands.

(iv) Stained particles in a few of the basal epidermal cells. Stained particles were not seen in the region of the pilomotor apparatus.

Abnormal skin. (i) *Normal skin pretreated with physical erythema-producing agents.*—Biopsy sections were removed during the course of erythema produced by ultra-violet, thorium-X, or Grenz irradiation, or by heat or cold. During the early stages, marked changes were noted in the location of staining, particularly in relation to the small arterioles. Collections of enzyme were detected both adjacent to, and within, the walls of all these vessels, as well as near the capillaries of the papillae. At the height of the erythema, in addition to these deposits, the enzyme was distributed in a linear fashion in the nerves of the superficial corium, including those branches which entered the epidermis. As the erythema declined and visible pigmentation appeared, stained particles were no longer detected around the blood vessels, or in the superficial nerves. The previous use of heat or cold produced similar results, although no staining was observed near capillaries after the use of cold.

During all these stages the entire basal layer of the epidermis showed a dense intracellular stain, which persisted for a longer period than did the intraneural stain, but eventually disappeared when pigmentation was well established. The previous use of heat or cold did not result in any increase in the basal cell content of stain.

(ii) *Psoriasis.*—All the cells of the epidermis involved in a lesion contained stained enzyme particles. The remainder of the enzyme distribution resembled that of normal skin.

(iii) *Eczema.*—Biopsies from these patients demonstrated the presence of periarteriolar stained particles about most of the small arterioles, and also

FIG. 2.—Nerve fibres demonstrating their content of cholinesterase. This is an aggregation about an eccrine sweat gland. Note that the enzyme deposits are not uniform throughout the nerve length, and that there are clumps at the visible ends of the nerves. That these are not the actual termini of the nerves may be seen by comparison with Fig. 1. Koelle. × 200.

in most of the basal epidermal cells ; staining was particularly heavy in the region of vesicles and around areas of inflammation. Out of interest, these cases were tabulated on the basis of the severity of the process, and from Table I a close parallel may be seen between the acuteness of the reaction and

TABLE I.—*The Relation of Epidermal Cholinesterase Content to the State of Eczema.*

State of eczema.	Number of cases.	Epidermal basal cells containing cholinesterase.					
		Centre of lesion.			Periphery of lesion.		
		All.	Many.	Occas.	All.	Many.	Occas.
Subacute	15	10	4	1	2	10	3
Chronic	23	12	9	2	6	6	11
Lichenified	4	0	2	2	0	0	4
Healing	11	1	6	4	0	0	11

the proportion of basal cells containing the enzyme. Disappearance of the cholinesterase coincided with clearing of the lesion. Occasional dermal cells also were observed to contain the enzyme.

(iv) *Urticaria.*—The distribution of stained fibres and deposits did not differ from that seen in normal skin with the exception of the nerve supply to the sweat glands. In the environs of apocrine glands the nerves were observed to contain cholinesterase in cholinogenic urticaria, in contrast to the unstained fibres of the normal skin. Thus in this type of urticaria, both apocrine and eccrine glands appeared to have a similar nerve supply.

(v) *Atopic dermatitis.*—Both linear and perivascular enzyme deposits were observed as in normal skin, together with intracellular stain in the basal cells of the epidermis at the site of lesions. In addition, numerous intracellularly stained cells were observed scattered through the superficial dermis near lesions, as had been noted in the cases of eczema.

Sections from cases of eczema and atopic dermatitis were stained with toluidine blue in an attempt to identify these stained cells as mast cells ; no such correlation proved possible. Biopsy material from a case of urticaria pigmentosa, stained with the cholinesterase stain and toluidine blue in consecutive sections, similarly failed to show any relation of these cells to mast cells. However, positive iron stains suggested that these cells were tissue macrophages containing haemosiderin. This was the only observation in which we obtained a positive thiocholine stain other than with cholinesterase. These results are summarized in Table II.

TABLE II.—*The Localization of Cholinesterase in Normal and Abnormal Skin.*

Diagnosis.	Epidermal nerves.	Dermal nerves.	Small arterioles.	Sweat glands. Apocrine.	Sweat glands. Eccrine.	Epidermal cells. Basal.	Epidermal cells. Other.
Normal	None	Occas.	Occas.	None	Present	Scant	None.
Erythema	Occas.	Almost all	Numerous	,,	,,	All	,,
Psoriasis	None	Occas.	Occas.	,,	,,	,,	All nucleated cells.
Eczema	,,	,,	Some	,,	,,	Most	In region of lesion.
Cholinogenic urticaria	Present	Present	,,	Present	,,	Scant	None.
Atopic dermatitis	None	Occas.	Occas.	None	,,	,,	In region of lesion.

DISCUSSION.

As Nachmansohn (1940) and Wybauw (1938) have separately pointed out, the biochemical investigations of Schoenheimer and numerous other workers have shown that the presence of any enzyme in tissue may be taken as presumptive evidence of the presence of its " unbound " natural substrate, since free

enzymes do not remain static in the tissues. Thus, the identification of acetylcholinesterase—the " specific cholinesterase "—in a tissue suggests the presence of free acetylcholine. The identification of non-specific cholinesterase does not permit us to deduce the presence of any other particular substrate so far known, since the physiological action of this enzyme has not yet been established. As a corollary to this theory, the failure to identify such an enzyme as cholinesterase histochemically does not necessarily indicate its total absence from the tissue under study, but may mean only that both the enzyme and its substrate are functionally inactive, existing then in a " bound " state (possibly adsorbed to protein).

On the basis of the differential staining technique employed in these examinations, it is suggested that most of the stain observed in nerve fibres and in relation to small arterioles is due to the presence of specific acetylcholinesterase, but that the intracellular stain observed in the epidermis is the result of its content of the non-specific type (Koelle, 1955). It must be further emphasized that the histochemical method here employed is not quantitative, so that no accurate assessment of the absolute quantities of the enzyme is made.

Sensory nerves.—It will be remembered that Weddell (1952) failed to confirm Von Frey's belief that specialized neural end-organs exist to subserve individual sensory stimuli by virtue of their specific structural adaptation. In the histologic observations which we have recorded, using the skin of the trunk and limbs, but not that of such specialized areas as the palms or lips, three forms of cutaneous sensory nerve endings were defined: Ramifying fibres ending freely in the corium; branches from these, whose finer twigs entered the epidermis, passing between the basal cells to end in the stratum granulosum; and fibres which terminated as arborizations about the bases of hair follicles. Few of these nerves were found to contain cholinesterase in a simple biopsy or after such a physiological stimulus as pressure on the site, but the enzyme did appear after the external induction of erythema by heat or cold, irradiation, or locally introduced chemicals such as atropine or Trafuril. It seems that the enzyme is present in sensory fibres, but that it does not function in the transmission of sensory impulses resulting from physiological stimuli; however, it is concerned in the so-called antidromic transmission occurring in sensory nerves as part of the mechanism of development of the flare response. This will be discussed later.

Our failure to demonstrate specialized nerve endings confirms Weddell's findings (Woollard *et al.*, 1940; Weddell *et al.*, 1952), in that no anatomically recognizable differentiation seems to exist in the types of nerve endings sensitive to various stimuli. The interpretation of the nature of the sensation is either by a central identification, or by a peripheral variation in the form of ensuing electrical discharge.

Appendages.—Although nerve fibres were demonstrated about the pilomotor

apparatus, none was found to contain cholinesterase, a finding in accord with the generally accepted opinion that these nerves are adrenergic in type.

In the case of sweat glands, there has been disagreement with regard to the form of innervation of apocrine glands. Shelley and Hurley (1953) in their investigations of innervation failed to obtain any evidence of cholinesterase-stained fibres about these glands, and thought that these glands at least were served only by adrenergic nerves from the sympathetic system. Aavik (1955), however, found the enzyme to be present in the nerves to both apocrine and eccrine glands. Rothman (1953), in his analysis of the two conflicting results, suggested that the apocrine glands had a dual innervation, primarily adrenergic, but capable of acetylcholine release in certain circumstances. In our own experiments, we found that under normal skin conditions, only the nerves supplying the eccrine glands contained cholinesterase. However, in cases of cholinogenic urticaria, the nerves supplying apocrine glands also contained cholinesterase, indicating that in this disorder there is an alteration in the functional neuronal pattern. Owing to the limitations imposed by this histochemical technique, no particular investigations could be carried out concerning the direct effect of acetylcholine in this disorder, but the preceding use of such materials as histamine and atropine failed to demonstrate any of the enzyme in the normal apocrine gland nerve supply. In order to reconcile the two points of view one may postulate that under normal conditions eccrine glands have a cholinergic nerve supply and apocrine glands an adrenergic one, but that in cholinogenic urticaria the nerves to the apocrine glands also contain cholinesterase. It may be pointed out here that after injecting nicotine (which prevents the postganglionic transmission of cholinergic impulses by a competitive blocking of acetylcholine) we have failed to demonstrate cholinesterase in the section of skin examined, although before biopsy clinical sweating in the area was noted.

Cutaneous Blood Vessels.—Until recently the innervation of cutaneous arterioles and metarterioles has been regarded as being solely through terminal fibres of the sympathetic nervous system, which by the release of epinephrin in the walls of the vessels effects vasoconstriction. This theory was however questioned as a result of Lewis's investigations into the triple response. In order to explain this phenomenon, he postulated the existence of antidromic vasodilator fibres, travelling with the sensory nerves, having their ganglion cells in the dorsal roots, and producing their effects through the release of "H-substance". It was observed that neither sympathectomy nor preganglionic section of sensory nerves altered their effects, but postganglionic section of these sensory nerves did result in a failure of the expected flare, provided a sufficient time lapse was allowed for degeneration of the nerves. In 1948, Euler identified acetylcholine in the walls of the normal larger arteries, indicating that there was some functional release of this substance, and

Thompson and Whittaker (1944) corroborated this by demonstrating both true and non-specific cholinesterase in the walls of medium-sized vessels. Studies carried out by Armin and Grant (1953) on the effects of denervation on arteries led them to postulate two forms of innervation, one having a vasoconstrictive action through the release of epinephrin, the other having a tonic dilating effect through the release of acetylcholine in the arterial wall, independent of central control. Pursuing this line of research, Hilton and Holton (1954) proposed that in the small cutaneous arterioles the release of acetylcholine from adjacent sensory nerve endings might provide a tonic vasodilator action by a local effect.

In our own sections of normal skin, although we frequently identified nerves adjacent to the small arterioles, none was observed directly to enter their walls. However, with enzyme stains we were able to identify cholinesterase in the small arteriolar walls as well as in the region of those vessels of the subpapillary plexus. After the development of an erythema (e.g., after irradiation), almost all the arterioles appeared to contain the enzyme intramurally, and it could also be demonstrated in the contiguous nerves. We have then evidence that whatever its source, cholinesterase, and presumably acetylcholine, is present in the walls of small arterioles, and is released in their vicinity under the stimulus of a developing erythema. This would imply that cholinergic nerves, if not directly supplying the vessel, at least affect its function by the local diffusion of acetylcholine. Since the only nerves demonstrated in this site were sensory ones, it suggests that the acetylcholine is derived from their terminals.

Responses to Intradermal Injections.

Clinical Responses.

Normal skin.—As a prototype of the form of response elicited in the cutaneous arterioles after injections, the triple response described by Lewis was produced in 10 patients by heavy linear pressure. The expected white line of vasoconstriction was observed, followed by the development of a surrounding flare. Histological sections from the area of pallor revealed no cholinesterase, but in the area of erythema cholinesterase was present in the walls of the small arterioles. Biopsies made at the time when this flare was fading failed to show any intramural enzyme.

Thirty normal patients were tested by the intradermal injection of acetylcholine, atropine, histamine, nicotine, and prostigmine, and also by the local application of Trafuril. After the introduction of histamine the injection wheal enlarged to a maximum in 5 minutes, and thereafter slowly disappeared within 20 minutes. This was the only material which produced such a whealing reaction. With both histamine and atropine a flare appeared about the site of injection within 2 minutes, spread to its maximum size in 5 minutes, and per-

sisted in all about 30 minutes. The injection of acetylcholine or prostigmine was followed by the rapid (1 minute) development of a flare lasting 5 to 10 minutes; a second deeper erythema developed in two-thirds of the patients immediately at the periphery of the injection wheal. This appeared in 5 to 10 minutes and lasted a further 20 minutes—until the wheal had disappeared.

The external application of Trafuril resulted in the appearance of a flare corresponding to the area treated. This developed in about 5 minutes and lasted for periods up to 4 hours. When nicotine was injected, a white area of vasoconstriction was observed at the site lasting for about 20 minutes. If the use of nicotine was followed by the introduction of any of the other 5 materials into the same site, the expected flares failed to appear. The prior injection of atropine delayed the subsequent development of flares with the other test substances, but the regular reactions proceeded after 10 minutes.

Irradiated skin.—Ten of these patients were retested after irradiation of the sites with ultra-violet, thorium-X, or Grenz rays. During the pre-erythema and early erythema phases, reactions were observed similar in character to the pretreatment ones, but appearing more rapidly, developing more floridly, and persisting for a longer period. Once the phase of full erythema was past, the expected flare failed to appear with any of the test substances, except acetylcholine. Nicotine gave its usual blanching. Repetition of the tests when pigmentation had developed disclosed a slow return to the normal form of skin response, in the order histamine, atropine, Trafuril, and prostigmine (Table III).

TABLE III.—*The Erythematous Response to Testing During the Course of Reaction to Irradiation.*

Stage of erythema.	Acetyl-choline.		Hist-amine.		Atropine.		Trafuril.		Prostig-mine.		Nicotine.	
	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.
Pre-erythema	10	0	10	0	10	0	10	0	10	0	0	10
Erythema	Difficult to observe because of state of skin.											
Post-erythema	10	0	1	9	0	10	0	10	0	10	0	10
Fading	10	0	7	3	6	4	4	6	0	10	0	10
Pigmentation	10	0	10	0	10	0	10	0	10	0	0	10

(P.—present. A.—absent.)

Eczema.—Tests were carried out in the area of eczematous reaction in each of 30 patients. Acetylcholine and nicotine gave their expected responses, but 75% of the cases had lost the normal flare to prostigmine, while approximately 66% failed to flare with atropine, and 50% with Trafuril—in about one half of these both reactions were absent in the same patient. There were also 3 patients in whom the usual flare with histamine did not develop; in none of these did the other materials induce flares, except acetylcholine, with which a normal reaction was evoked. In an attempt to establish a relationship between the state of the eczema and the type of reaction obtained, we classified

the condition of each patient with regard to the severity of his dermatosis, and retested 10 of them as healing progressed (Table IV). It appears from these results that the more acute eczematous reaction was associated with a greater variation from the normal in the forms of skin test responses, and that as healing occurred the reactions tended to return to normal. No " weeping " dermatosis was tested.

TABLE IV.—*The Variation in Intradermal Test Responses During the Course of Eczema.*

Test substance.	State of flare.	State of Eczema.			
		Subacute.	Inactive.	Healing.	Healed.
Acetylcholine	Present	10	10	10	10
	Absent	0	0	0	0
Histamine	Present	7	8	10	10
	Absent	3	2	0	0
Atropine	Present	6	8	10	10
	Absent	4	2	0	0
Trafuril	Present	6	8	9	10
	Absent	4	2	1	0
Prostigmine	Present	0	2	7	10
	Absent	10	8	3	0
Nicotine	Absent	10	10	10	10

Urticaria.—All the patients with urticaria gave normal types of reactions with the skin tests, but usually more florid than in normal patients. In addition to histamine, both acetylcholine and Trafuril produced whealing in this group.

Atopic dermatosis.—Observations were made both in uninvolved and involved skin. Of the 30 atopic patients tested, one half showed a " delayed blanch " reaction after the injection of acetylcholine. This type of response was characterized by the absence of an initial erythema after the injection, and the appearance, in about 3 to 5 minutes, of a visible area of pallor surrounding the injection wheal ; this usually lasted 10 minutes. None of the group who gave this response developed a flare with any of the other test materials. In addition, a further 5 patients showed a paling or vasoconstrictive response with histamine, although their reaction to acetylcholine was normal. None of these 5 showed any flare with the remaining test materials, with the exception of one patient who had a flare after atropine. The other 10 patients demonstrated the variations in eczematous areas which have been previously described in those patients with eczema ; almost all reverted to the normal reactions once the lesions had cleared.

Linear pressure was used in an attempt to produce the triple response, as had been done in the normal group. In the atopic patients with an abnormal reaction to acetylcholine and histamine, no flare was seen at the periphery of the central stroke, but in its place a slowly developing area of pallor was noted. This abnormal reaction was a constant feature whether the skin was clear or diseased. Most of the remaining 10 gave this reaction on an eczematized area, but they all also gave a normal reaction at some subsequent examination.

Histochemical Responses.

Studies were conducted using the Koelle stain on biopsies from the peripheral sites of reaction in all those patients in whom skin tests were done. With acetylcholine and prostigmine most of the enzyme content would be used up, so that no stain is seen at the site.

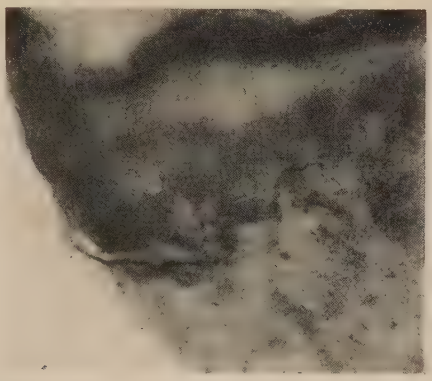

FIG. 3.—Specific acetylcholinesterase in the substance of a dermal nerve fibre, some of whose branches enter the epidermis. The dense stain in the background and in the basal epidermis is due to non-specific cholinesterase. Normal skin pretreated with Trafuril. Koelle. × 200.

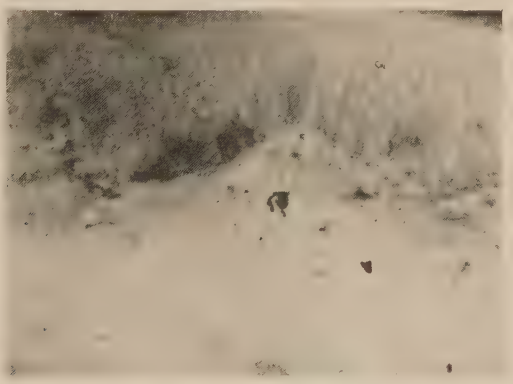

FIG. 4.—A clumped deposit of acetylcholinesterase in and around the wall of a small arteriole of the dermis. The small trail of stain extending deeper into the dermis indicates the presence of the nerve supplying the area. Biopsy taken during the normal flare after atropine injection. Koelle. × 200.

Normal skin.—Biopsies done at the sites of erythema induced by the various materials showed enzyme deposits in and about most of the small arterioles of the superficial dermis. In addition to these perivascular collections, atropine- and Trafuril-treated skins showed accumulations of enzyme within the dermal and epidermal nerves (Figs. 3 and 4). After the injection of nicotine no enzyme concentrations were observed. In biopsies of skin treated with

Trafuril, almost all the epidermal basal cells contained aggregations of enzyme.

Irradiated skin.—Where a flare was still obtainable—chiefly during the pre-erythema phase—no difference in enzyme localization was noted. In the later post-erythema phase, when flares failed to develop, enzyme was not detected, except in the basal epidermis as in the untested skin subjected to irradiation.

Eczema.—Where the normal flare was visible in response to the injected material, enzyme was demonstrated in the environs of small arterioles. In those skins which failed to show a clinical erythematous response, no enzyme was noted histologically, except for the basal epidermal cell content noted previously.

Urticaria.—The biopsies from these cases gave normal findings.

Atopic dermatosis.—An interesting situation was observed in these cases. Enzyme deposits were noted about the small arterioles in those subjects who developed a flare after their intradermal injection. In contrast to the patients with eczema who showed no enzyme at all in non-flaring skin, atopic patients revealed cholinesterase in the same sites as in normally flaring skin. As in our other tests the previous use of nicotine resulted in the total absence of enzyme from the sections.

Sections from the area of pallor about the site of stroking used to demonstrate the unusual form of triple response showed no cholinesterase. All these results are summarized in Table V.

Discussion.

Functional Units.

In attempting to explain the mechanism of the vascular triple response, Lewis proposed the existence of the axon reflex as the functional pathway for the distal part of the antidromic vasodilator system. The axon reflex appears to be independent of central control, involving one or more branches of a cutaneous sensory nerve. The most distal point of ramification is conceived of as behaving as a functional ganglion cell, while the two arms of the reflex arc consist of one or more distal branches of the same parent nerve. Thus the distal branches may act interchangeably as receptor or effector arms for the reflex. This concept has been named the " Skin-Nerve Unit " by Rothman. Such an axon reflex may provide the mechanism of the flare seen adjacent to areas of injury, inflammation, or eczematous change. The nature of the chemical release associated with these nerves has not been satisfactorily determined. Wybauw (1936) demonstrated the liberation of acetylcholine in the tissues following antidromic stimulation, while Lewis suggested that acetylcholine did not act directly on blood vessels, but rather on cells in the basal layer of the epidermis, which in turn released histamine to affect the

TABLE V.—*The Comparison of Responses in Normal and Abnormal Skin to Test Substances.*

Test substance.	Vascular reactions.	Diagnosis. Normal. Number of cases.	Normal. Cholinesterase. Present.	Normal. Cholinesterase. Absent.	Eczema. Number of cases.	Eczema. Cholinesterase. Present.	Eczema. Cholinesterase. Absent.	Atopic. Number of cases.	Atopic. Cholinesterase. Present.	Atopic. Cholinesterase. Absent.
Acetylcholine	Flare—									
	Early	30	—	—	30	—	—	15	—	—
	Late	21	—	—	10	—	—	0	—	—
	Blanch	0	—	—	0	—	—	15	—	—
Histamine	Flare—									
	Present	30	30	0	27	26	1	10	10	0
	Absent	0	—	—	3	0	3	20	20	0
Trafuril	Flare—									
	Present	30	30	0	14	14	0	5	5	0
	Absent	0	—	—	16	0	16	25	24	1
Atropine	Flare—									
	Present	30	30	0	10	10	0	11	10	1
	Absent	0	—	—	20	0	20	19	16	3
Prostigmine	Flare—									
	Present	30	—	—	8	—	—	9	—	—
	Absent	0	—	—	22	—	—	21	—	—
Nicotine	Flare—									
	Present	0	—	—	0	—	—	0	—	—
	Absent	30	0	30	30	0	30	30	0	30

(P.—present, A.—absent.)

vessels. Gilman (1946) in his review of the subject is in accord with this hypothesis although postulating that the initial vasodilatation is due to the direct action of acetylcholine. In this connection, the identification of cholinesterase in the cells of the basal epidermis provides a possible indication of the pathways concerned.

The Mechanism of Erythema Production.

The mechanism of the production of erythema, either by mechanical stroking, irradiation, or by locally introduced chemicals, may involve either a direct action upon the effector organ—the blood-vessel wall—or an indirect effect through the regional nerves in an axon reflex. In the triple response to stroking, the vasoconstriction at the point of stimulation appears to be the result of a direct effect on the small arterioles and capillaries, but the surrounding erythema is likely to be the result of an axon reflex, since cholinesterase is demonstrable in the local nerves and arterioles.

Undoubtedly, several of the chemical compounds may directly alter the reacting tissue; for instance, histamine is known to effect dilatation of metarterioles and precapillary sphincters. However, there are several observations which suggest that a nervous pathway plays the major part in producing

the vascular effects of these various stimuli. Procaine can abolish the erythema if injected locally prior to the test ; similarly both nicotine and atropine, which appear to act as local anaesthetics in raising the threshold of response to acetylcholine, prevent the response of erythema. Finally the use of these six provocative agents resulted in the appearance of cholinesterase in most of the cutaneous nerves. We must then consider that the development of erythema is largely dependent upon the local nerve supply. Further, since recent proximal nerve section and anaesthetic nerve block do not interfere with the observed effects, the local axon reflex appears to be the transmitter of the impulse resulting in vasodilatation. The effect of acetylcholine appears to be a combination of an indirect axon reflex-produced erythema—the initial flare—and a local direct chemical action on the arteriolar wall after diffusion—the later flare developing in the periphery of the injection wheal.

In the normal subject the development of erythema from whichever of those stimuli used was associated with the presence of cholinesterase in the nerves and about adjacent small arterioles. A similar finding was observed in the mechanically produced triple response. This indicates that the acetylcholine-acetylcholinesterase system is concerned in the neural mechanism for the production of erythema, but whether this association is one of cause and effect, or a concurrent one, cannot be decided. Recent investigations suggest that adenosine triphosphate is the substance primarily concerned in impulse transmission along the nerve fibre, and that acetylcholine is secondarily released, thereby achieving alterations in membrane permeability. Its fortuitous release terminally in the fibre may then be considered part of the same phenomenon, by which diffusing acetylcholine will reach the regional small arterioles (Holton and Holton, 1953).

Abnormal Vascular Responses.

There were three groups of subjects in whom a variation from the normal triple response erythema was observed—normal subjects who were in the post-erythema phase after irradiation, patients with subacute or chronic eczema, and cases of atopic dermatosis. Those in the first and second groups are distinguished by the persistence of the normal flare of the triple response, and a normal flare with the introduction of acetylcholine, although there is much variation in the reactions to the other test materials. The third group may be divided into two sections ; about half behaved in a fashion similar to the chronic eczematous patients, while the remainder gave a " white response " to stroking, a delayed blanch with acetylcholine, and no flare whatsoever after the use of the other materials.

In the post-irradiation state, maximal dilatation of small arterioles is thought to exist, and is attributed to a state of refractoriness due to the presence of released proteases, histamine, acetylcholine, and tissue metabolites (Whitfield,

1938). The vessels are presumed therefore to be incapable of further response. Although the particular reasons for such a state have not been demonstrated by any investigators, the theory is in accord with our observation of the absence of vascular response to most of the chemicals used, and the absence of any histochemical evidence of cholinesterase. The fact that acetylcholine itself could still elicit a normal response suggests that it presents a stimulus sufficient to affect the small arterioles directly.

In subacute and chronic eczema, Whitfield first described a state of increased contractile excitability, although the reasons for such a state have not been adequately defined. Certainly, with the exception of acetylcholine, most of the chemicals failed to elicit the normal response and no cholinesterase was seen histochemically : this suggests that the neurovascular mechanism is out of action, as a result either of changes in tissue permeability or of the presence of counter-effective tissue metabolites. Acetylcholine itself was still capable of producing a normal response, so that the arteriolar wall itself was still affected directly.

It is likely that a similar explanation accounts for the abnormal reaction observed in those atopic patients who had a normal acetylcholine response, but such an assumption cannot be made in the case of the remaining 50%. Here we observed : (i) Blanching in place of flaring in the triple response, unassociated with the presence of cholinesterase ; (ii) failure of flare after the use of histamine, prostigmine, Trafuril, and atropine, despite the identification of tissue cholinesterase ; (iii) a delayed blanching after the injection of acetylcholine. Clinically this group presents the complete atopic syndrome, consisting of skin pallor, lowered peripheral temperatures, rapid and excessive response to the cold pressor test, a delayed response to heating, and cutaneous—including facial—oedema (Russell and Last, 1955).

If one can ignore for a moment the absence of *visible* erythema after the test injections, and assume that the histochemical evidence of cholinesterase (and consequently, acetylcholine) is associated with vasodilation as it is in all the other test situations, one may then ask why the vasodilatation cannot be seen. The most obvious explanation is oedema, and here we have several observations to assist us, It has long been noted that vasodilator responses are not so readily obtainable in the leg, nor are they observed in patients with cardiac or nephrotic oedema, although once the oedema is relieved, the normal vascular reactions are again obtained. It has also been observed that the local application of hydrocortisone or the general administration of steroids for a short period will result in the disappearance of the flare responses in the normal skin (Kalz *et al.*, 1957). These steroids cause the interstitial accumulation of water through their salt-retaining properties. In other words, the existence of oedema *per se*, from whatever cause, is associated with failure to observe normal vasomotor reactions. Acting on this hypothesis, we infiltrated test

areas in atopic patients with hyaluronidase and found that, provided this material was employed in sufficient concentration, erythematous responses were produced to the various test materials injected into the prepared site, just as in the normal subject (Fig. 5). The injection of nicotine after hyaluronidase did not result in a flare response, and hyaluronidase was not found to alter the expected reactions in the normal patient. Once the effects

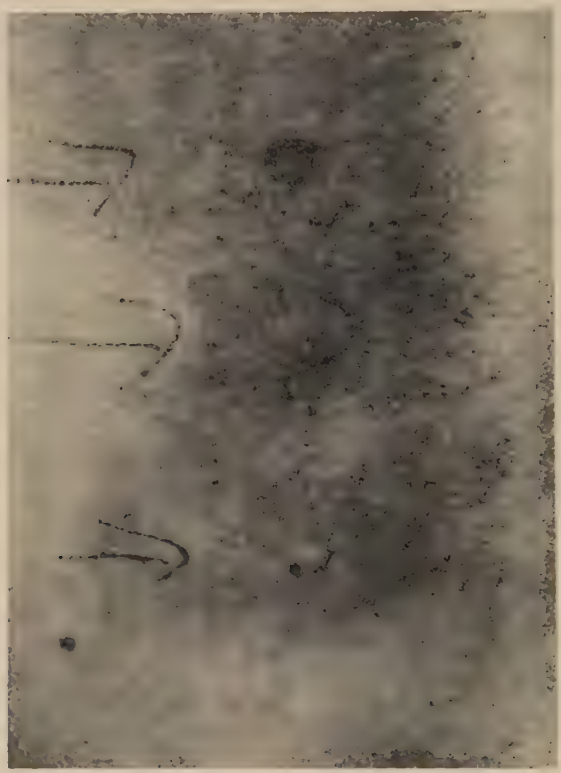

FIG. 5.—The skin response of an atopic patient to histamine alone (upper arrow), histamine after a previous injection of hyaluronidase, and acetylcholine after previous injection of hyaluronidase (lower arrow). Note the absence of a flare with histamine alone, and its appearance with both histamine and acetylcholine after the use of hyaluronidase. Also note that the skin is not involved in the dermatosis.

of this enzyme had disappeared, the test flares were no longer obtainable in the atopic. These results suggest that vasodilatation does indeed occur in the atopic as in the normal subject, but that coexistent oedema prevents it being seen.

It is also possible that the delayed blanching effect observed after the injection of acetylcholine is due to the slowed diffusion of this material because of local oedema, so that the direct effect of acetylcholine on small arterioles is achieved by only a minimal quantity of the substance, thereby creating a

situation analogous to that described by Burn (1950) in the rabbit's ear, after acetylcholine has been leached out.

As has been mentioned, many investigators have shown that acetylcholine is normally synthesized in vessel walls. Burn has suggested that this acetylcholine may act as a local hormone, bound to protein, and exerting a tonic influence upon the vessel wall. If this is true, then it might be hypothesized that an increased concentration of bound acetylcholine in the arteriolar walls of atopic patients is responsible, in them, for the same phenomenon of motor stimulation as has been observed experimentally: Prolonged perfusion of vessels with acetylcholine leads to vasoconstriction; all available protein has bound the incoming acetylcholine, so that the normal synthesis has been depressed. The addition of further acetylcholine only serves to induce further constriction of vessel walls, while epinephrin would relieve the excessive effect of acetylcholine.

A disruption of the normal acetylcholine-acetylcholinesterase function would interfere with the vessel wall permeability which is thought to be controlled to some extent by this chemical system, thereby permitting the interstitial oedema associated with atopy.

Conclusions.

1. Sensory nerve terminations in the trunk and limbs are represented not as specialized end-organs, but by fibrils ending freely in the superficial dermis, the deeper epidermis, and about hair follicles. Sensory discrimination thus depends on either functional impulse variations within the nerve fibre, or central neuronal identification.

Specific acetylcholinesterase was identified within sensory fibres, but appeared to be concerned, not with sensory impulse transmission, but with the passage of antidromic impulses concerned in axon reflexes induced by mechanical (stroking), physical (ultra-violet rays), or chemical (histamine, etc.) means. The presence of this enzyme appears to be related directly to the production of erythema, but is not necessarily causally concerned in the transmission of the nerve stimuli.

2. Motor autonomic nerves arborize about all the sweat glands. Under normal conditions, only those nerves supplying the eccrine glands contain free acetylcholinesterase. Only in one state—viz., in cholinogenic urticaria—did the apocrine gland nerve supply contain this enzyme.

3. Nerves terminating about the pilomotor apparatus did not have any demonstrable acetylcholinesterase present within them.

4. No nerve fibres ended within the substance of arteriolar walls, but sensory nerve terminals were adjacent to most of them.

5. Under normal conditions only occasional small arterioles contained specific acetylcholinesterase in the walls, but in the presence of erythema induced

by stroking, irradiation or chemical means, this enzyme was present in all the arteriolar walls and at the termini of the adjacent sensory nerves. It appeared that the acetylcholinesterase reached the vessels by diffusion through tissue. As remarked above, the presence of acetylcholinesterase (and consequently, of acetylcholine) seemed causally related to the production of erythema.

6. Non-specific cholinesterase was present in occasional basal epidermal cells of normal skin, but in all the basal cells in skin affected by irradiation, eczematization, Trafuril, and urticaria. Psoriatic lesions were unique in that the entire epidermis contained cholinesterase deposits.

7. The structural form of the cutaneous nerves was not disturbed by any of the tests used, nor in any of the dermatoses studied.

8. In general, the skin followed the pattern of Lewis's triple response in its reactions to test materials, such as histamine, Trafuril, prostigmine, atropine, and acetylcholine. This reaction consisted of a central wheal (with an injection) and a surrounding vasodilatation with visible erythema, associated with the appearance of free acetylcholinesterase in the sensory nerves and in the small arterioles. The use of acetylcholine demonstrated a minor variation in that this substance had a direct effect on the vessels as well as an indirect one via the usually involved axon reflex.

For the most part these tests provide a means of testing (*a*) the integrity of the local axon reflex, (*b*) the responsiveness of the local vasculature, (*c*) the degree of permeability of the tissue tested.

9. In the group of patients studied there were three states in which abnormal test reactions were elicited—post-irradiation, eczematization, and atopy. In the first two conditions, the normal response was obtained only with acetylcholine. The variation from normal in the other tests appeared to be due to lack of response of small arterioles. The alterations observed in the responses of the third group were due to the presence of tissue oedema, and could be prevented by the use of hyaluronidase.

10. Although no conclusion can be reached with regard to the basic disorder in atopy, it may be suggested that an excess of bound acetylcholine in the vessel wall serves to depress synthesis of this material to such an extent that arteriolar constriction results, with altered vascular permeability.

I should like to thank Dr. G. C. Wells, in whose laboratory I started this investigation, and Dr. R. M. B. MacKenna, whose suggestions and assistance enabled me to continue the study at St. Bartholomew's Hospital.

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RADIO-ACTIVE SODIUM ABSORPTION STUDIES IN ERYTHROCYANOSIS CRURUM PUELLARUM FRIGIDA.

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Erythrocyanosis crurum puellarum was first described under this heading by Klingmüller (1921); a similar condition, erythema induratum atypicum, was described by Denecke (1919). This disease has been described by other authors under various titles (Lengfellner, 1922; Thibierge and Stiassnie, 1921; Bolte, 1922; Poor, 1926; Karwowski, 1927).

Klingmüller (1921) carefully studied the clinical aspects of erythrocyanosis and concluded that it belonged to the perniosis group of disorders; he also reported keratosis pilaris in association with this condition, and the elephantiasic thickening of the supra-malleolar tissues which may occur. He thought that oedema may be responsible for the follicular hyperkeratosis. Mendes da Costa (1926) described the familial incidence of the malady, and Lengfellner (1922) and Klingmüller and Dittrich (1930), mention the ulceration which may develop. It has been noted that erythrocyanosis may sometimes be associated with Bazin's disease, but most authors do not consider tuberculosis to be the primary aetiological factor in erythrocyanosis. Poor (1926) noticed that many cases of erythrocyanosis were first seen at the menarche, and Bolte (1922) favoured an endocrine basis for the disease.

Klingmüller and Dittrich (1930) described the condition on the calves of women and young girls and associated it with the current fashion in dress. They believed that cold had an irritant effect on the smaller vessels of the skin. The degree of cold necessary to provoke the change might be slight. On repetition of exposure to cold, organic irreversible changes occurred in the blood vessel walls. They did not favour the name erythrocyanosis crurum puellarum since they said the changes may be seen on the buttocks of males. Lewis (1936) also thought that the condition was due to fashion of dress: "it came in with short skirts and thin stockings and will go out with them". Marchionini (1954), in his article on "Clothing and its significance in the pathogenesis of skin diseases in Anatolia", makes the observation that "the wide trousers worn by women prevent the occurrence of Erythrocyanosis crurum

puellarum, an affection frequently seen in North and Central Europe ". Dore and Stott (1922) and Parkes Weber (1925) also blamed scanty covering of the legs and Dickson Wright (1933) said the condition was commoner in Scotland, though he did not enlarge on the significance of this. Goldsmith (1936) considered that cold was of much less importance in erythrocyanosis than in chilblains, and some of his cases were worse, or presented, in the summer.

Telford (1933, 1937) held the view that there was no basic difference between erythrocyanosis crurum puellarum frigida, and the erythrocyanosis seen in a leg paralysed by poliomyelitis. In the poliomyelitis limb there was a decreased venous return, and at operation for lumbar ganglionectomy he noted that the external iliac arteries were narrow, and might be no thicker than the radial arteries (probably due to disuse of the limb). These limbs were very fat and nodules and ulcers occurred where the subcutaneous fat was thickest. He stated that thin legs were almost immune from this change and thought that Bazin's disease was in no way different from erythrocyanosis in its basic pathology. Percival and Stewart (1927) believed that ulceration in erythrocyanosis was always due to mechanical trauma and drew attention to the fact that the subjects were usually " plump, flabby and inactive ".

Boyd (1950) has described the erythrocyanosis type of swollen leg, and considers that in these cases the vessels (arteries and veins) are invariably hypoplastic ; he has demonstrated narrow arteries and veins by arteriography and venography (personal communication).

The condition has been studied clinically by earlier authors in considerable detail. Klingmüller and Dittrich (1930) have examined histological sections and have made capillary microscope studies on the skin of erythrocyanotic patients. Lewis and Love (1926) investigated the vascular responses of the skin to cold by calorimetry and skin thermometry.

Following the description of the use of radio-active sodium (^{24}Na) in investigation of the local circulation by Kety (1948, 1949) it appeared feasible to compare ^{24}Na clearance rate in cases of erythrocyanosis and in normals. Radio-active phosphorus has been used by Seeberg (1947) in absorption studies, and both these methods may be regarded as an elaborate form of the Aldrich and McClure test (1923).

According to Kety (1948) the clearance rate of ^{24}Na, injected as sodium chloride, from a tissue is largely dependent on the local circulation. The clearance rate depends on :

(i) The arterial flow per unit mass of tissue.
(ii) The tissue sodium space.
(iii) Lymphatic outflow.
(iv) Diffusion rate of ions, and diffusion distances.
(v) Capillary-tissue interface.
(vi) Proportion of arterio-venous shunts, or non-functional blood flow.

Stone and Miller (1949) have confirmed the assumption that lymph flow does not contribute significantly to the tissue clearance of ^{24}Na. Despite much experimental work by Braithwaite *et al.* (1954), McGirr (1952), Franke *et al.* (1950), Wisham *et al.* (1951), Wisham and Yalow (1952), and many other authors, the role of the capillary-tissue interface and the diffusion rate of ^{24}Na in the extravascular space remained obscure until the work of Gemmell and Veall (1956). These authors have extensively reviewed the literature, and have designed experiments to show that if the ^{24}Na clearance rate is measured at 37° C. then changes at the capillary-tissue interface (produced by histamine injection) and changes in diffusion rates (produced by hyalase injection) have no significant effect on the clearance rate.

Miller and Wilson (1951) found that ^{24}Na clearance rate and the blood circulation rate as measured by calorimetry did not run parallel. This may well be explained by the fact that the experiments were conducted on the hand where a large number of arterio-venous anastomoses are known to be present.

Gemmell and Veall (1956) believe that, at 37° C. the ^{24}Na clearance rate is a measure of the volume of plasma flowing through capillaries in unit time per unit volume of extracellular fluid in the tissue under test. Since the tissue sodium space remains constant in a normal patient, within the physiological range, the clearance rate is directly proportional to the capillary blood flow per unit time, per unit mass of tissue.

Accepting the validity of these conclusions, we decided to use the ^{24}Na clearance rate to compare the circulation times in erythrocyanotic patients and in a control group.

Investigation.

Material and Method.

Twelve cases of erythrocyanosis of varying severity affecting the calves and ankles of young women were studied. Their ages ranged from 20–35 years. They had all attended the skin department for erythrocyanosis, or had complained of it while they were attending for some other malady. Since the number of cases diagnosed in the outpatient department is a small percentage of the total female patients attending, short skirts and thin stockings are unlikely to be the sole aetiological agents. The menstrual histories of these patients were not abnormal, and among the worst affected were two girls with slim legs. No clinical evidence of hypothyroidism was found. Two had suffered from blisters, and two had suffered from hypodermal nodules. The controls were females within the same age range as the cases of erythrocyanosis.

The subject was placed lying on a couch in a room where the ambient temperature was 22° C.–24° C. Sandbags were placed on each side of the ankles and a Geiger-Muller counter supported on a burette stand was mounted over the area to be examined. A G.M.4 end-window tube was used counting γ

radiation. The thermo-couples of a Cambridge skin thermometer were applied to constant sites on the ankles. With the counter in position the legs were covered by an electric heat cradle. After twenty minutes' rest, the cradle was switched on and the temperature of the lower legs and feet was raised to 37° C. and maintained at this level. After a further fifteen minutes, an intracutaneous injection of radio-active sodium was given into a point 2 in. above the ankle joint on the anterior surface of the leg. The injected volume was 0·05 ml. and contained approximately 1·0 microcurie of ^{24}Na as isotonic sodium chloride solution. A tuberculin syringe with a hypodermic 20 needle was used. Any leak back was carefully mopped dry, and the Geiger counter was centred $\frac{1}{2}$ in. above the site of injection as soon as all seepage had ceased.

The counts were recorded by a " Panax " ratemeter and transferred on to graph paper by an automatic pen writing recorder (Elliott). Readings were taken from this graph and plotted logarithmically against time at $\frac{1}{4}$-minute intervals, the readings having been corrected for any background count. The readings on the recorder fall off following an exponential curve ; but when plotted logarithmically give a straight line graph. The slope of this line was expressed as $T_{\frac{1}{2}}$. This value is the time, in minutes, taken for the initial recorded value to fall to half, and was used as an index of the clearance rate. The $T_{\frac{1}{2}}$ value obtained by this method showed a 10% variation on repeated tests in the same patient. (Three readings at weekly intervals were taken in two normal cases, and two readings at four weeks interval were taken in two cases of erythrocyanosis.) This was considered to be sufficiently constant, since the percentage of difference between normals and erythrocyanosis cases was approximately 100%. These results are shown in Table I.

TABLE I.

Normal controls.		Erythrocyanosis.	
Patient	$T_{\frac{1}{2}}$	*Patient*	$T_{\frac{1}{2}}$
Tu	4·0	Ts	6·25
Ro	3·75	Hi	6·25
He	3·75	Ho	8·00
Ti	4·50	Gr	8·25
Fo	4·25	Te	11·00
Ba	4·00	Bar	6·00
We	5·00	Gu	6·75
McC	4·25	Br	6·00
MoE	3·75	Sl	7·50
Ga	4·75	Ja	5·50
		Hil	13·50
		Ru	7·00

These results were subjected to statistical analysis and were found to be highly significant ($t = 4·57$).

CONCLUSIONS.

Under conditions of maximum vasodilatation the ^{24}Na clearance rate is significantly slower in erythrocyanotic patients than in a group of normal

controls of similar age and sex. It may therefore be deduced that under these conditions the local blood flow rate is slower in cases of erythrocyanosis than in normal subjects.

It may be that abnormal reaction to cold causes permanent damage to the arterial supply to the skin or perhaps, as Boyd (1950) has suggested, these vessels are developmentally narrow in cases of erythrocyanosis. Further work to elucidate the part played by chilling in this disease is planned.

These observations show that the skin circulation may be given a numerical index for a particular site under certain strictly controlled conditions.

We should like to thank Dr. W. N. Goldsmith for his interest in the investigation, and Dr. P. J. Hare for sending us cases to examine. We are most grateful to Dr. H. Payling Wright for the loan of apparatus, and for her helpful advice.

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PITYRIASIS RUBRA PILARIS IN IDENTICAL TWINS.

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(Chief: Professor Poul V. Marcussen, M.D.)

De Beurmann, Bith and Heuyer (1910) seem to be the first to have described the familial occurrence of pityriasis rubra pilaris (Devergie's disease).

In 1942 Touraine collected 148 cases of pityriasis rubra pilaris (P.R.P.), of which at least 62 (42%) were familial.

Leitner (1947) reviewed altogether 152 cases, including 6 of his own patients with this disease, which corresponds roughly to Touraine's material. Leitner considers the disease to be invariably hereditary, assuming as is probably correct, that there exist mild cases which are not diagnosed.

On the other hand Zeisler (1923), Touraine, and later Kierland and Kulwin (1950) hold that there exist two types of the disease—an hereditary form manifesting itself in childhood, and an acquired form emerging in middle age, with no genetic relation, but apart from this not different from the former type.

P.R.P. does not seem to have been previously described in identical twins.

Case Reports.

The patients are identical twin girls, born on 6 July 1946.

The parents and the older brother are in good health, and there are no other known cases of skin disease and more particularly P.R.P. in the family.

Apart from ordinary children's diseases the patients have on the whole been well, and have not suffered from skin complaints in earlier childhood.

The children were 10 years old at the first consultation. In the child (G.) that came first to be examined some changes in the legs resembling neurodermatitis had been developing since early in 1956. The twin sister (E.) had noticed affection of back and neck since July 1956, which was immediately diagnosed as P.R.P. Now it was possible to revise the diagnosis of G., as it turned out that she, too, had typical though less pronounced changes of neck and body.

On 12 February 1957, both patients were sent to the department for treatment. At this stage the disease had developed in both of them. G. had developed more marked and extended changes on the body, though they were still less than those found in E., who by now had involvement of the legs practically identical with that of her sister.

On examination.—Typical follicular keratoses with spicula, one millimetre long, localized to neck and back, but most pronounced on pigmented skin and in places exposed to pressure. On the shins and around the ankle joints were symmetrical, almost continuous, scratched lichenifications with large rectangular scales, but only just perceptible follicular keratosis. Neither here nor on the back was the colour particularly typical, though during a short period it was a rather characteristic brick-red.

On examination 4 months later the legs were about equally affected. Only a few follicular keratoses were observed on the pigmented part of the upper arms, and the trunk was by then practically smooth.

During the observation period of about one year the condition fluctuated somewhat, but at no time was the skin completely normal. Typical lesions on fingers, backs of the hands, palms, soles, or scalp were not observed. Nails unaffected.

No general symptoms. Routine laboratory tests normal. Standard patch tests and protein tests (scarification) negative. The minimal erythema dose after 24 hours : 1 minute (Hanau mercury arc lamp with the spectral lines : 2970, 3020, and 3130Å. No filter. Lamp-skin distance : 50 cm. The irradiated field was on the back.)

Treatment consisted of the usual dermatological local treatment and Bucky-rays (in a limited field) with some alleviation of pruritus. Lomholt (1947) described the beneficial effect of carbon arc light, but we withheld this because the pigmented portion of the skin was especially affected.

Comments.

Leitner's survey includes genealogical tables of 15 families in which two or more cases of P.R.P. have occurred. These are analysed in a separate section by Ford, who concludes that P.R.P. is probably always dominantly inherited ; it is therefore to be expected in half the offspring of a diseased person and in half the members of an affected family of sisters and brothers. Ford, however, attaches particular importance to three genealogical tables (in the original report referred to as Figs. 5, 8, and 9), where the parents of those affected do not suffer from the complaint, though in other respects the familial tendency is obvious at least in two of the cases. Ford suggests this might arise either by mutation, or if heterogeneous carriers of the disease may themselves be normal (i.e. the dominance would be incomplete). Mutation can be ruled out in one case (Fig. 5) and thus cannot account for all cases. Besides, the disease is so rare that the number of cases approaches the mutation frequency of the population. One of Leitner's own cases was not diagnosed until the patient was about 40, in spite of frequent medical examinations and objective symptoms ; cases occurring in relatives may evidently be missed, and for this reason the " solitary " cases may perhaps also be hereditary.

The lesions of P.R.P. in identical twins described here were mild, and the disease was diagnosed in one child only when the sister was also examined. It is noteworthy that no other cases of P.R.P. are known in this family. Hence, it must be assumed that the disease has arisen through mutation or through a normal heterogeneous carrier ; or alternatively that other members of the family have or have had the disease but so mildly that it has escaped notice.

Summary.

A case of pityriasis rubra pilaris in ten-year-old identical twins is described. The familial cases of the disease described in literature are briefly referred to, and its genesis is discussed.

These patients were presented to the Danish Dermatological Society at its meeting on 7 March, 1957.

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—Dr. L. Forman.

21 March 1957.

Multiple Self-healing Epitheliomata.—Dr. D. E. Oakley.

This patient was presented at the meeting of the British Association of Dermatology at Birmingham in 1955 with his daughter as examples of multiple familial self-healing squamous cell carcinomata. He was then aged 41 and his daughter aged 18.

The father was first seen by me in 1947 with a long history of nodules in his skin which had gradually regressed over the years while fresh lesions made their appearance. In the summer of 1955 he had several hazel-nut sized tumours on his thighs and buttocks and there were many scars of previous lesions on his face, arms and legs.

In December 1956 he attended with a nodule on the right shin which was larger than those previously seen, and which showed early fungation. It was decided to treat this with radium. The tumour responded well, and when seen on 27.i.57 had flattened down and no longer appeared active. All his other lesions were in various stages of regression except one on the back which had a granulating appearance. In the course of this consultation he complained of a lump in the rectum ; proctoscopy revealed nothing beyond a small fissure in ano, and higher up a ring of piles. He was referred to a surgeon, who did a sigmoidoscopy and found a carcinoma at 13 cm. completely encircling the bowel. Abdomino-perineal excision was performed, followed by a stormy aftermath, including chest complications and a paralytic ileus culminating in rupture of his abdominal incision. He died during the operation for repair of the rupture.

Post-mortem showed multiple carcinomatous deposits in the liver and lungs, reported as adeno-carcinoma.

Discussion.

The President : Do you think there is any relationship between the skin carcinoma and that developing in the bowel, comparable to the multiple skin and bowel carcinomata that may occur after the ingestion of inorganic arsenic ?

Dr. Oakley : At first all the lesions healed spontaneously ; then there was one that was apparently not healing. Then shortly after the patient developed carcinoma of the bowel and died. It perhaps suggests a relationship.

Dr. C. D. Calnan : I think Dr. Ferguson Smith's original patient died of cancer, but there was no proof it was related to one of these lesions. I am not at all sure there is any proved record of a fatal case.

Dr. A. Girdwood Fergusson : There are six cases I know of personally. One is a patient of my own who has been suffering from a Ferguson Smith syndrome, I am certain, for 20 years ; and the other five cases have been suffering from the same thing for varying periods. They are still producing these self-healing tumours. Some take a long time to heal, some a comparatively short time. Although Dr. Ferguson Smith's first case died—I was R.M.O. in the department at the time—there was no connexion between the cause of death and the skin.

Neurofibromatosis and Malignant Pericytoma.—Dr. O. L. S. Scott.

This girl is 20 years old. She was first seen by me 2 years ago, on account of a mild degree of xeroderma. She also had early lesions of neurofibromatosis as they have been seen to-day. The next occasion when I saw her was this month, when I learned that she had noticed in the meantime a swelling of the left forearm in August 1956. As it

was growing larger, she saw her doctor, she was referred to a surgeon and a tumour was excised in December 1956, about the size of a walnut, as the surgeon put it. The next month, i.e. last January, it was noticed that the tumour was recurring locally. She was given x-ray treatment with no obvious benefit.

When I saw her the tumour was much the same size as to-day, about 3 × 2 inches. I presumed it was a fibrosarcoma associated with her neurofibromatosis, and I obtained the section from the original operation and showed it to Dr. Haber. He made a diagnosis of haemangiopericytoma, and he will kindly describe the histology presently.

Before he does so, however, there is one question that arises. Is this very rare tumour related in any way to her genetically determined neurofibromatosis ? I have discussed this with anatomists and zoologists—for neurofibromatosis exists in cows, horses, dogs and deer. They all agree that there is an association. They believe that this tumour may originate in the Pacinian corpuscles. These Pacinian corpuscles are pressure nerve endings found in tendon sheaths, aponeuroses, intermuscular septa, periosteum, peritoneum, pleura, pericardium, mesentery and dermis of palms and soles. When they are deformed by pressure, impulses pass up the nerves. The corpuscles resemble an onion with concentric lamellar capsules around a central space in which is contained the nerve fibre and a minute vessel (Todd and Bowman quoted by Johnston, 1935). The inner surfaces of the lamellae are lined by endothelial cells. The pericytoma may arise from these endothelial cells or from the vessels, and the resemblance between the diagrams shown and the histological section is striking. These tumours are usually benign, but Stout's figures (1955) show that about 11% of cases produce metastases. In this case there is little doubt.

Dr. Whimster tells me that he has seen this type of histology post mortem in mesenteric and retroperitoneal tumours arising in patients with neurofibromatosis. He says that it is one of the many forms which a so-called " retro-peritoneal sarcoma " may take.

Dr. H. Haber : This is a very interesting tumour. It shows spindle-shaped cells in close apposition and surrounding characteristically vascular lumina. The tumour would qualify for a diagnosis of Haemangiopericytoma.

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Liver Disease with Pigmentation and Diabetes Mellitus.—Dr. O. L. S. Scott.

A man aged 72, a Latvian.

On holiday at the seaside in August last year he became sunburnt. Three weeks later he developed severe generalized itching and jaundice which had persisted for 3 months when he was first seen by Dr. John Richardson, under whose care he was admitted to hospital. He was then found to have generalized yellow-brown pigmentation, enlarged liver and spleen, and diabetes mellitus. A provisional diagnosis of carcinoma of the head of the pancreas was made and the possibility of haemochromatosis also was considered.

Skin histology showed increased melanin pigmentation in the epidermis, but there was no siderosis.

Liver biopsy showed multilobular cirrhosis of the liver.

The liver function tests, which were impaired, have shown gradual improvement, and the enlargement of the liver and spleen have beome somewhat less. His clinical condition has generally improved.

Comment.—Although carcinoma of the pancreas cannot be entirely ruled out at this stage without a laparotomy or further biopsies, this man appears to belong to that group of patients described by Whitlock (1951). Whitlock had 4 cases of melanin pigmentation with liver disease; two of them also had diabetes mellitus. He considered

that the primary disorder lay in the failure of the cirrhotic liver to detoxicate oestrogens. The accumulated oestrogens then might stimulate melanogenesis *via* the pituitary or directly by neutralizing the action of glutathione in the skin, thereby releasing tyrosinase to oxidize DOPA. Dr. Whitlock tells me that he is no longer entirely convinced of this theory, but that he cannot think of another explanation to offer.

Discussion.

Dr. J. S. Pegum: This case has some of the features of xanthomatous biliary cirrhosis, a disease which occurs largely, if not entirely, in middle-aged women in which there is pigmentation first of all and then a pre-xanthomatous eruption. The latter is intensely irritable and consists in the cases described by Ahrens *et al.* (1950) of papules which have had their tops scratched off. After that the patients tend to become jaundiced. This is associated with an enlarged liver, but with a histology different from that reported in this case. It would be interesting, incidentally, to know what the blood cholesterol and lipoids are in Dr. Scott's case.

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Dermabrasion.—Dr. J. S. Pegum.
Dermabrasion.—Mr. Patrick Clarkson.
Tuberculides—Dr. O. L. S. Scott.
Dermal Leishmaniasis.—Dr. R. G. Howell.
Sarcoidosis with an Unusual Arthritis.—Dr. C. M. Ridley.

BOOK REVIEWS

The Year Book.*

This excellent publication continues to live up to its standard of usefulness, containing abstracts with comments of a large proportion of the dermatological literature of the year.

In this edition the authors' contribution is on the subject of eczematous contact dermatitis. The Dermatology School of New York has, for many years, shown a particular interest in cutaneous allergy so that a contribution from these authors on the subject is of exceptional value. In the present number they deal principally with general considerations and diagnosis, leaving other aspects of the subject to be dealt with in some future edition.

Successful abstracting is extremely difficult. This *Year Book*, like its predecessors, encompasses this task most excellently ; it seems impossible to suggest any improvement in the style and method which these authors adopt. F. R. B.

Dermatology for Nurses.†

This text-book for nurses begins with a very helpful introduction. Although the discomfort and incapacity caused by severe skin diseases is obvious, it is often only when nurses have seen a considerable number of skin patients that they are able to realize what monstrous proportions even a minor lesion may assume, and the need to deal kindly though firmly with their patients.

The book should prove of principal value to nurses in India and other tropical countries. In warm climates the nursing techniques and problems of skin treatment are somewhat different from those encountered in temperate zones and for this reason dermatological nursing methods evolved in Europe and North America may not always be applicable. A book of this sort, written by one with experience in tropical dermatology, is designed to meet the needs of those countries. It will also no doubt be of value to nurses who have trained in temperate climates and go to practise in the tropics. G. E. N.

Occupational Dermatoses.‡

It is ten years since the previous edition of this book appeared and as the authors say in the preface " The new chemicals and new methods of manufacture which are so rapidly and constantly being evolved bring with them new skin hazards to workers engaged in their manufacture and in their application, as well as to the public who use products containing these chemicals ". This edition effectively covers the new processes and the authors have largely concentrated on these. It is inevitable that with increasing knowledge both of skin hazards and of preventive measures, the harmful processes of ten or twenty years have been superseded wherever possible ; at the same time, new problems have arisen. In spite of this, the same table of Yearly

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* *The Year Book of Dermatology and Syphilology* (1956–7 Series). R. L. Baer and Victor H. Witten. Chicago : The Year Book Publishers. London : Interscience Publishers Ltd. Pp. 464. Figs. 62. Price 53*s*.

† *Dermatology and Venereology for Nurses*. P. N. Behl (1957). Delhi : Pitambar Book Depot. Pp. 125. Figs. 68. Price 10 Rupees.

‡ *Occupational Diseases of the Skin*. L. Schwartz, L. Tulipan and D. J. Birmingham (1957). London : Henry Kimpton. 3rd. Ed. Pp. 981. Illus. 189. Price £6 10*s*. 0d.

Prevalence of Occupational Dermatoses by Industries is given as in the first edition which was published in 1939. This may be because no later figures are available or because the overall incidence of skin disease in the various industries listed has not changed appreciably in this time.

The general format of this edition follows that of its predecessors. The first few chapters deal with the broad outlines of the problem and there is an excellent chapter on the diagnosis of industrial skin disease. The chapter on methods of investigation of these conditions deals chiefly with the details of conducting actual investigations in factories and is a most useful guide to anybody who may have to undertake this important duty. Among methods of prevention, the modern views on the difficult subject of barrier creams and skin cleansers are discussed.

There is a fascinating chapter on Occupational Marks by F. Ronchese and in keeping with the emphasis on new processes, W. D. Norwood contributes a full chapter on Skin Hazards from Radiation in Atomic Industry, Medicine and Defence. The rest of the book follows the pattern of the previous editions. Dermatoses produced by various substances are as far as possible considered in related groups and there is a comprehensive survey of the skin hazards of different occupations—no fewer than one hundred and fourteen are discussed. A surprising omission to English eyes is coal mining.

Although compensation laws differ in different countries, the chapter on the Medico-legal Aspects of Occupational Dermatoses should be read carefully by any physician who may have to give evidence in a case of this sort. The warnings of the pitfalls which a clever lawyer can engineer are clearly emphasized, and the trials and tribulations of such questions as patch-testing and allergy are written by one who has great experience of the ordeal of the witness-box.

It is surprising that one of the characteristics of occupational skin cancer listed is that they usually do not have metastases and one wonders whether the basis of this statement is that in the past many cases of keratoacanthoma were diagnosed as skin cancer. Incidentally, this condition, which is relatively common in this country, is not mentioned in the book. Another minor criticism is the inclusion of the potent sensitizer, benzocaine, in the prescription of a soothing cream for the treatment of burns.

Such slight imperfections have to be looked for carefully and the authors are to be congratulated on this third edition which has, if possible, improved on its predecessors. It must have a place on the desk of every practising dermatologist in this Industrial Age.

H. R. V.

CURRENT LITERATURE.

ROLE OF TRANQUILIZING DRUGS IN ALLERGY. B. C. Eisenberg. (1957) *J. Amer. med. Ass.*, **163**, 934.

Patients with asthma, eczema or hay fever or other symptoms considered to be of allergic origin were treated with chlorpromazine, reserpine or meprobamate. The percentage of patients to whom the treatment was of benefit ranged from 37% with meprobamate to 21% with reserpine, as compared with 10% of controls. The author suggests that the drugs relieve psychiatric states, which tend to aggravate the physical symptoms. A. J. R.

ALLERGENICITY OF TRANQUILIZING DRUGS. C. Bernstein and S. D. Klotz. (1957) *J. Amer. med. Ass.*, **163**, 930.

The side-effects of three of the most widely used tranquilizing drugs are reviewed. Reserpine rarely gives rise to true sensitivity. Flushing, urticaria and nasal congestion suggest a histamine-like response. Chlorpromazine can cause dermatitis, photosensitivity, pruritus, agranulocytosis (less than 0·3%) jaundice (0·8–1·4% of patients using the drug for more than a week). Meprobamate has become available more recently. Reactions reported include angioneurotic oedema, urticaria, fever, joint swelling and tenderness and purpura. A. J. R.

ECCHYMOTIC SKIN LESIONS IN PATIENTS RECEIVING PREDNISONE. C. W. Denko and L. R. Schroeder. (1957) *J. Amer. med. Ass.* **164**, 41.

Purpura and ecchymosis occurred in 20% of 75 patients receiving prednisone for various rheumatic disorders. Platelet and coagulation studies were within normal limits, but capillary fragility was increased. A. J R.

LICHEN SCLEROSUS ET ATROPHICUS IN CHILDREN. Marvin E. Chernosky, Vincent J. Derbrs and James W. Burks, Jnr. (1957) *Arch. Derm. Syph., Chicago*, **75**, 647.

The authors add two to the 35 cases already reported. All occurred in females and symptomatology and histopathology were as in adult cases. No effective treatment was found and prognosis is uncertain as no case has been followed well into adult life and through the childbearing age. J. K.

SOME HISTOCHEMICAL OBSERVATIONS ON THE HUMAN ECCRINE SWEAT GLANDS: II. THE PATHOGENESIS OF MILIARIA. Richard L. Dobson and Walter C. Lobitz, Jnr. (1957) *Arch. Derm. Syph., Chicago*, **75**, 653.

The histology of artificially produced miliaria does not always show the structure described by O'Brien. The present investigation shows that the initial anatomical alteration in experimental miliaria is plugging of the sweat pore with Schiff-positive, diastase-resistant material. This leads to degeneration of the epidermal portion of the sweat duct and the formation of a parakeratotic " keratin plug ". If sweating continues a self-perpetuating process is established. J. K.

SIX YEARS' SURVIVAL IN SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS. AN ANALYSIS OF TWELVE CASES. John R. Haserick. (1957) *Arch. Derm. Syph., Chicago*, **75**, 706.

Not all patients with severe systemic lupus erythematosus survive even with modern treatment, and it is not yet possible to present a statistical evaluation of any treatment programme. One patient first seen in 1948 has received no steroid hormone therapy and yet is in excellent health to-day. Others were given in addition to cortisone or A.C.T.H. various drugs such as anti-malarial drugs or nitrogen mustard. The author considers that these have a place in the treatment of this disease but steroid therapy should be continued for as long as it is necessary to control the disease and until a natural remission occurs. Steroid therapy is not indicated in mild forms of systemic lupus erythematosus. J. K.

CONVERSION OF CAROTENE TO VITAMIN A BY SEBACEOUS GLANDS. Ruven Greenberg, Theodore Cornbleet and Ronald Demovsky. (1957) *Arch. Derm. Syph., Chicago,* **76**, 17.

A suspension of carrot oil was injected into the dermis of men and rats. Fluorescent microscopy of biopsy specimens taken 30 minutes to 72 hours later showed the presence of vitamin A in the sebaceous glands, in the sebum and in a thin layer upon the epidermis. The concentration of vitamin A in rats was much less than in man. A similar experiment with crystalline carotene showed in man no detectable amount of vitamin A after 30 minutes and only trace amounts after 72 hours. No vitamin A was demonstrated in rats after injection of crystalline carotene.

The authors consider that the presence of vitamin A on the surface of the skin may affect the mitosis of epidermal cells. J. K.

THE DIAGNOSIS OF LUPUS ERYTHEMATOSUS: PROBABLE SIGNIFICANCE OF PANTOTHENATE BLOOD LEVELS. Albert H. Slepyan, D. V. Frost, L. R. Overby, R. L. Fredrickson and Arnold E. Osterberg. (1957) *Arch. Derm. Syph., Chicago,* **75**, 845.

The authors found that the ratio of bound/free pantothenic acid levels in patients with discoid and systemic lupus erythematosus and with lymphoblastoma were abnormally low. This preliminary study indicates that this test may be of great help in differential diagnosis.

J. K.

PROTEOLYTIC ACTIVITY IN PEMPHIGUS: I. THE PELS-MACHT TEST. John W. Dougherty, Frank E. Cormia and Shirley A. Unrau. (1957) *Arch. Derm. Syph., Chicago,* **75**, 793.

It is considered that the phytotoxic effect of pemphigus serum on *Lupinus albus* seedlings is due to increased proteolytic activity of the serum. This activity may reside entirely in the fibrolysin fraction or be associated with other serum proteases and serum proteolytic enzyme inhibitors. Refutation of the Pels-Macht test is based upon work done at room temperature when fibrolysin is rapidly deactivated. The present experiments were carried out in a refrigerator at 55–60° F. (It must be assumed that " room temperature " in New York is somewhat higher).

J. K.

ACUTE PORPHYRIA AND COPROPORPHYRINURIA FOLLOWING CHLOROQUINE THERAPY. Michael J. Davis and Darl E. Vander Ploeg. (1957) *Arch. Derm. Syph., Chicago,* **75**, 796.

PORPHYRIA CUTANEA TARDA: REPORT OF CASE SUCCESSFULLY TREATED WITH CHLOROQUINE. Irving D. London. (1957) *Arch. Derm. Syph., Chicago,* **75**, 801.

In the first article two cases are recorded; the one a mixed type of hepatic porphyria and also discoid lupus erythematosus, the other porphyria cutanea tarda. Both patients showed marked exacerbatiou of the symptoms of porphyria after the administration of chloroquine but improved when the drug was stopped.

The second article recounts how the symptoms of porphyria cutanea tarda disappeared after the patient was given chloroquine. He has remained clear for a year.

J. K.

OCCURRENCE OF LATE SYPHILIS IN UNTREATED SYPHILITIC PATIENTS. Jozef Towpik. (1957) *Brit. J. vener. Dis.*, **33**, 2.

In Poland the introduction of modern methods of venereal disease control, based on a new epidemiological approach, has reduced the incidence of syphilis from 50 per 10,000 population in 1947 to 0·97 in 1955.

This paper is based upon a study of 4000 patients, with different forms of late syphilis, who were seen and examined during the period 1950–55.

Many interesting facts emerge and the paper should be read in detail to be fully appreciated.

W. G. A.

ON THE TREATMENT OF EARLY FORMS OF SYPHILIS. N. S. Smelov. (1957) *Brit. J. vener. Dis.*, **33**, 16.

A most informative paper which should be read in detail by all practising venereologists, in order to appreciate the number of difficulties and unsolved problems with which we are still faced, and these include the proper role of antibiotics in the therapy of syphilis. W. G. A.